Complete Summary

GUIDELINE TITLE

(1) Diagnosis and management of epilepsy in adults. A national clinical guideline.
(2) Diagnosis and management of epilepsy in adults. Update to printed guideline.

BIBLIOGRAPHIC SOURCE(S)

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70). [295 references]

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. Update to printed guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004 Jun 7. 3 p. [1 reference]

GUIDELINE STATUS

This is the current release of the guideline.

Any amendments to the guideline will be noted on the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Epilepsy
- Status epilepticus

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Family Practice
Internal Medicine
Neurology
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Public Health Departments
Social Workers

GUIDELINE OBJECTIVE(S)

To provide evidence based recommendations on the diagnosis and treatment of epilepsy, including recommendations on initial antiepileptic drug (AED) treatment, management of drug-resistant epilepsy, management of status epilepticus, management of provoked seizures, management of people with learning disability and epilepsy, and contraception, pregnancy, and menopause

Note: Epilepsy in the elderly is addressed only indirectly. Other text exists detailing the management of epilepsy in the elderly and after stroke.

TARGET POPULATION

Adult patients with epilepsy or status epilepticus

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Patient history, including what occurred before, during, and after the attack
2. Electroencephalography (EEG)
3. Magnetic resonance imaging (MRI)
4. Computed tomography (CT) scanning

Treatment

1. Antiepileptic drugs (AEDs), such as carbamazepine, sodium valproate, lamotrigine, and oxcarbazepine monotherapy
2. Combination therapy of AEDs
3. Short-term benzodiazepine treatment
4. Psychological treatments
5. Referral for assessment for neurosurgical treatment
6. Intravenous (IV) lorazepam or diazepam for immediate treatment of generalised tonic-clonic status epilepticus
7. Fosphenytoin with electrocardiography (ECG) monitoring or phenytoin with electrocardiography monitoring or phenobarbital for sustained control if seizures continue in generalised tonic-clonic status epilepticus
8. Rectal diazepam

Note: Liver function and full blood count should not be monitored routinely.)

Contraception, Pregnancy, and Menopause Management

1. Oral contraception with oestrogen
2. Barrier methods of contraception
3. Folic acid
4. Vitamin K_1 intramuscularly at birth for infant born to mother taking enzyme-inducing AEDs
5. Betamethasone for women taking enzyme-inducing AEDs with preterm labour threat
6. Intravenous lorazepam or diazepam for seizures during labour

Note: The progesterone-only contraceptive is not recommended for women taking enzyme-inducing AEDs.

Note: Progesterone implants are not suitable for women taking enzyme-induced AEDs.

Note: Hormone replacement therapy [HRT] should be prescribed for the same indications as in women who do not have epilepsy.

MAJOR OUTCOMES CONSIDERED

- Seizure frequency
- Seizure severity scales
- Adverse events
- Neuropsychological assessment
- Quality of life
- Seizure control
- Neurological disability
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The evidence base for this guideline was synthesised in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Healthstar, Cinahl, PsycINFO, and the Cochrane Library. The year range covered was 1996-2001. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, the United Kingdom (UK) Health Technology Assessment programme, and the United States (US) National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN Web site, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group. All selected papers were evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies, e.g. case reports, case series

4: Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Scottish Intercollegiate Guidelines Network (SIGN) carries out comprehensive systematic reviews of the literature using customized search strategies applied to a number of electronic databases and the Internet. This is often an iterative process whereby the guideline development group will carry out a search for existing guidelines and systematic reviews in the first instance and, after the results of this search have been evaluated, the questions driving the search may be redefined and focused before proceeding to identify lower levels of evidence.

Once papers have been selected as potential sources of evidence, the methodology used in each study is assessed to ensure its validity. SIGN has developed checklists to aid guideline developers to critically evaluate the methodology of different types of study design. The result of this assessment will affect the level of evidence allocated to the paper, which in turn will influence the grade of recommendation it supports.

Additional details can be found in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [UK]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50]), available from the SIGN Web site.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The process for synthesizing the evidence base to form graded guideline recommendations is illustrated in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [UK]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50], available from the SIGN Web site.

Evidence tables should be compiled, summarizing all the validated studies identified from the systematic literature review relating to each key question. These evidence tables form an important part of the guideline development record and ensure that the basis of the guideline development group's recommendations is transparent.

In order to address how the guideline developer was able to arrive at their recommendations given the evidence they had to base them on, SIGN has introduced the concept of considered judgement.

Under the heading of considered judgement, guideline development groups are expected to summarise their view of the total body of evidence covered by each evidence table. This summary view is expected to cover the following aspects:

- Quantity, quality, and consistency of evidence
- Generalisability of study findings
- Applicability to the target population of the guideline
- Clinical impact (i.e., the extent of the impact on the target patient population, and the resources need to treat them.)

Guideline development groups are provided with a pro forma in which to record the main points from their considered judgement. Once they have considered these issues, the group are asked to summarise their view of the evidence and assign a level of evidence to it, before going on to derive a graded recommendation.

The assignment of a level of evidence should involve all those on a particular guideline development group or subgroup involved with reviewing the evidence in relation to each specific question. The allocation of the associated grade of recommendation should involve participation of all members of the guideline development group. Where the guideline development group is unable to agree a unanimous recommendation, the difference of opinion should be formally recorded and the reason for dissent noted.

The recommendation grading system is intended to place greater weight on the quality of the evidence supporting each recommendation, and to emphasise that the body of evidence should be considered as a whole, and not rely on a single study to support each recommendation. It is also intended to allow more weight to be given to recommendations supported by good quality observational studies where randomised controlled trials (RCTs) are not available for practical or ethical reasons. Through the considered judgement process guideline developers are also able to downgrade a recommendation where they think the evidence is not generalisable, not directly applicable to the target population, or for other reasons is perceived as being weaker than a simple evaluation of the methodology would suggest.

On occasion, there is an important practical point that the guideline developer may wish to emphasise but for which there is not, nor is their likely to be, any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline as "good practice points." It must be emphasized that these are not an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Grade A: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or randomized controlled trial rated as 1++ and directly applicable to the target population; or

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

Grade B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

Grade C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rate as 2++

Grade D: Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Good Practice Points: Recommended best practice based on the clinical experience of the guideline development group.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A national open meeting is the main consultative phase of the Scottish Intercollegiate Guidelines Network (SIGN) guideline development, at which the guideline development group presents their draft recommendations for the first time. The national open meeting for this guideline was held in November 2001 and was attended by around 150 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN web site for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

The guideline was reviewed in draft form by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline.

The guideline was then reviewed by an Editorial Group comprising relevant specialty representatives on SIGN Council, to ensure that the peer reviewers' comments had been addressed adequately and that any risk of bias in the guideline development process as a whole had been minimised.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): In June 2004 the Scottish Intercollegiate Guidelines Network (SIGN) released an update to this guideline, available on the SIGN Web site . The only change to the following recommendations is denoted below in bold italics.

Note from SIGN and NGC: In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the full-text guideline document.

The grades of recommendations (A-D) and levels of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) are defined at the end of the "Major Recommendations" field.

Diagnosis

Who should make the diagnosis of epilepsy?

C: The diagnosis of epilepsy should be made by a neurologist or other epilepsy specialist.

Classification

C: The seizure type(s) and epilepsy syndrome should be identified.

C: The distinction should be made between a focal epilepsy and an idiopathic generalised epilepsy.

Clinical Factors and Diagnosis

C: A clear history from the patient and an eyewitness to the attack give the most important diagnostic information, and should be the mainstay of diagnosis.

Use of Electroencephalography (EEG) in the Diagnosis and Classification of Epilepsy

C: Electroencephalography (EEG) is not routinely indicated and should not be performed to "exclude" a diagnosis of epilepsy.

C: EEG can be used to support the diagnosis in patients in whom the clinical history indicates a significant probability of an epileptic seizure or epilepsy.

C: EEG should be used to support the classification of epileptic seizures and epilepsy syndromes when there is clinical doubt.

C: EEG should be performed in young people with generalised seizures to aid classification and to detect a photoparoxysmal response.

C: Video EEG and other specialist investigations should be available for patients who present diagnostic difficulties.

Brain Imaging

C: Magnetic resonance imaging (MRI) is the modality of choice for brain imaging in patients with epilepsy.

C: Brain imaging is not routinely required when there is a confident diagnosis of an idiopathic generalised epilepsy and if there is rapid and complete response to the first line antiepileptic drug.

D: Computed tomography (CT) has a role in the urgent assessment of seizures, or when magnetic resonance imaging is contraindicated.

Treatment

When and by Whom Should Antiepileptic Drug (AED) Treatment be Commenced?

B: The decision to start antiepileptic drugs (AEDs) should be made by the patient and an epilepsy specialist.

AEDs should be offered after a first tonic-clonic seizure if:

- B: The patient has had previous myoclonic, absence or partial seizures
- B: The EEG shows unequivocal epileptic discharges
- B: The patient has a congenital neurological deficit
- D: The patient considers the risk of recurrence unacceptable

Antiepileptic Drug Monotherapy

A: Carbamazepine, sodium valproate, lamotrigine and oxcarbazepine can all be regarded as first-line treatments for partial and secondary generalised seizures.

A: Sodium valproate and lamotrigine are drugs of choice for primary generalised seizures and should also be prescribed if there is any doubt about the seizure types and/or syndrome classification.

A: The side effect and interaction profiles should direct the choice of drug for the individual patient.

Note: Formulations of AEDs are not interchangeable and generic substitution should not be employed. All antiepileptic drugs licensed for monotherapy have similar efficacy in newly-diagnosed epilepsy.

Management of Drug-resistant Epilepsy

C: Failure to respond to appropriate AEDs should prompt a review of the diagnosis of epilepsy and adherence to medication.

A: Combination therapy should be considered when treatment with two first line AEDs has failed or when the first well-tolerated drug substantially improves seizure control but fails to produce seizure-freedom at maximal dosage.

B: The choice of drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three AEDs.

Antiepileptic Drug Blood Levels

D: Routine monitoring of AED concentrations is not indicated. Measurement can sometimes be useful in the following circumstances:

- Adjustment of phenytoin dose
- Assessment of adherence and toxicity

D: Assay of lamotrigine, vigabatrin, gabapentin, topiramate, tiagabine, oxcarbazepine and levetiracetam concentrations should not be undertaken routinely.

Management of Provoked Seizures

B: Short term benzodiazepine treatment may be given to reduce the risk of seizures in the context of acute alcohol withdrawal and delirium tremens.

B: Following an acute brain insult or neurosurgery, prophylactic AED treatment is not indicated.

C: Following an acute brain insult, AEDs used to treat the provoked seizures should be withdrawn (unless unprovoked seizures occur later).

D: AED treatment is not indicated for concussive convulsions.

Antiepileptic Drug Side Effects

C: Patients should be warned of potential side effects and given clear instructions to seek medical attention urgently for symptoms including rash, bruising or somnolence with vomiting especially in the first weeks of treatment.

D: Patients taking AEDs should receive dietary and other lifestyle advice to minimise the risk of osteoporosis.

C: Liver function and full blood count should not be monitored routinely.

Antiepileptic Drug Withdrawal

A: Prognostic index indicators can be used to give an estimate of the risks of seizure recurrence following AED withdrawal (refer to tables 2 and 3 in the original guideline document).

Psychological Treatment of Epilepsy

B: Psychological treatments are not an alternative to pharmacological treatments, but their use can be considered in patients with poorly controlled seizures.

Surgical Referral

B: Referral for assessment for neurosurgical treatment should be considered if the epilepsy is drug resistant.

D: Assessment as to suitability for a potentially curative resective procedure should be made before consideration of palliative procedures such as vagus nerve stimulation.

Management of Status Epilepticus

Immediate measures

D: In the community or in hospital, patients with generalised tonic-clonic status epilepticus should be managed immediately as follows (with local protocols being in place):

- Secure airway
- Give oxygen
- Assess cardiac and respiratory function
- Secure intravenous (IV) access in large veins

A: Give lorazepam 4 mg IV or diazepam 10 mg IV if lorazepam is unavailable. This can be repeated in hospital after 10 minutes if there is no response. If there is a delay in gaining IV access in the community: give diazepam 10-20 mg rectally (rectal solution or IV solution).

D: In hospital:

- Collect blood for full blood count, urea and electrolyte, liver function tests, calcium, glucose, clotting, AED levels and storage for later analyses
- Measure blood gases to assess extent of acidosis
- Establish aetiology. Give 50 ml 50% glucose IV if there is any suggestion of hypoglycaemia and IV thiamine (given as Pabrinex two pairs of ampoules) if there is any suggestion of alcohol abuse or impaired nutritional status

Within 30 minutes

D: For sustained control in patients with established epilepsy, within 30 minutes:

- Give usual AED treatment orally or by nasogastric tube (or IV if necessary for phenytoin, sodium valproate and phenobarbital).

B: For sustained control in other patients or if seizures continue, within 30 minutes:

- Give fosphenytoin in a dose of 18 mg/kg phenytoin equivalent (PE) IV, up to 150 mg/min with electrocardiography (ECG) monitoring; or phenytoin 18

mg/kg IV, 50 mg/min with ECG monitoring or phenobarbital 15 mg/kg IV, 100 mg/min. Rates of infusion may need to be reduced if hypotension or arrhythmia occur or in elderly or renal/ hepatic impairment.

Longer than 30 minutes

D: If status persists, then within 60 minutes:

- Admit to intensive treatment unit (ITU) and administer general anaesthesia
- Monitor using EEG to assess seizure control
- Refer for specialist advice

Non-convulsive status epilepticus

D: Patients with non-convulsive status epilepticus should be managed as follows:

- Maintain or reinstate usual oral AED treatment
- Consider lorazepam 4 mg IV or diazepam 10 mg IV
- Refer for specialist advice

Patients with recurrent prolonged or serial seizures in the community

A: Patients with recurrent prolonged or serial seizures in the community should be initially managed by carers who should give diazepam 10-20 mg rectally according to an agreed protocol (protocols must include advice on when to transfer to hospital).

Management of People with Learning Disability and Epilepsy

D: In the management of people with learning disability and epilepsy:

- Adequate time should be allowed for the consultation
- The carer should know the patient and bring relevant information on seizure type, frequency, possible side effects of medication, general health and behaviour to the consultation
- Information in an accessible form should be available to clients and carers
- There should be a multidisciplinary approach to treatment, delivered by professionals with an expertise in epilepsy, to improve quality of life. Community learning disability nurses have an important role in liaising between the specialist services and clients and carers

Advice on Rectal Diazepam or Equivalent Emergency Medication

D: All carers of patients with learning disability and epilepsy who may require rectal diazepam, should receive recognised training in its administration. Retraining should take place every two years.

D: A care plan should be drawn up in consultation with the general practitioner (GP) and/or specialist service, used by everyone working with the individual client, and reviewed at regular intervals.

D: Adequate support and instruction should be given to families.

Contraception, Pregnancy and Hormone Replacement Therapy (HRT)

Contraception

Combined oral contraceptive (COC)

D: When the combined oral contraceptive is given with an enzyme-inducing AED, one containing a minimum of 50 micrograms of oestrogen should be used; women should be warned that its efficacy is reduced and barrier methods of contraception should also be used if maximal contraceptive effect is required.

D: If breakthrough bleeding occurs with 50 micrograms of oestrogen the dose should be increased and "tricycling" of the combined oral contraceptive should be considered.

Progesterone-only contraception

D: The progesterone-only oral contraceptive is not recommended for women taking enzyme-inducing AEDs.

D: Depot injections of progesterone may be used with enzyme-inducing AEDs but should be given every 10 weeks.

D: Progesterone implants are not suitable for women taking enzyme-inducing AEDs.

Emergency contraception

D: The dose of levonorgestrel for emergency contraception should be increased to 1.5 mg and 750 micrograms 12 hours apart in women taking enzyme-inducing AEDs.

Preconceptual Counseling

Risks to the fetus from maternal epilepsy

D: Women should be made aware of the risks of uncontrolled seizures both to themselves and to the fetus.

Risks to the fetus from antiepileptic drugs

C: If AEDs are to be used in pregnancy the relative risks of seizures and fetal malformation should be discussed with the woman.

C: Whenever possible, a woman should conceive on the lowest effective dose of one AED appropriate for her epilepsy syndrome. If she has good seizure control and presents already pregnant, there is probably little to be gained by altering her AEDs.

D: Any woman who has given birth to a child with a malformation while taking AEDs should be offered review by an epilepsy specialist before becoming pregnant again.

Folic acid

D: All women with epilepsy should be prescribed a daily dose of 5 mg folic acid from preconception until the end of the first trimester.

Vitamin K_1

C: All infants born to mothers taking AEDs should be given vitamin K_1 1 mg intramuscularly at birth.

D: If there are additional risk factors for haemorrhagic disease of the newborn (e.g., maternal liver disease, anticipated premature delivery) oral vitamin K_1 (phytomenadione 10 mg daily) should also be given in the last month of pregnancy.

Pregnancy

D: If preterm labour is threatened in women taking enzyme-inducing AEDs, 48 mg betamethasone (double the normal dose) should be given over 48 hours.

AED doses and blood level monitoring during pregnancy

D: Dose of AEDs should not be increased routinely in pregnancy but should only be adjusted on clinical grounds.

Labour

D: The usual oral AED medication should be continued during labour and postnatally. In women unable to tolerate oral medication, AEDs can be given by other routes.

Seizures in labour

D: Seizures in labour should be terminated as soon as possible using intravenous lorazepam or diazepam. If seizures persist, manage as for status epilepticus.

Risks of inheriting epilepsy

Febrile convulsions

D: A comprehensive family history of epilepsy should be taken and expert advice on the genetics of epilepsy should be available as required.

Hormone replacement therapy (HRT)

D: Women should be aware that their seizure pattern may change at the time of the menopause.

D: Hormone replacement therapy should be prescribed for the same indications as in women who do not have epilepsy.

Models of Care

Models of Primary and Shared Care for Epilepsy

D: A structured management system for epilepsy should be established in primary care. As with other chronic diseases, an annual review is desirable.

D: The annual review would be facilitated and enhanced by the deployment of specialist epilepsy nurses, linking primary care to the hospital system (shared care).

D: The shared care management system adopted should seek to:

- Identify all patients with epilepsy, register/record basic demographic data, validate the classification of seizures and syndromes
- Make the provisional diagnosis in new patients, provide appropriate information and refer to a specialist centre
- Monitor seizures, aiming to improve control by adjustment of medication or re-referral to hospital services
- Minimise side effects of medications and their interactions
- Facilitate structured withdrawal from medication where appropriate, and if agreed by the patient
- Introduce non-clinical interventions, and disseminate information to help improve quality of life for patients with epilepsy
- Address specific women's issues and needs of patients with learning disabilities

Information for Discussion with Patients and Carers

Advice and Information on Epilepsy

D: A checklist should be used to help healthcare professionals to give patients and carers the information they need in an appropriate format (refer to the original guideline document for an example information checklist).

Outcome measures

Seizure Frequency

D: Assessments should always include seizure frequency and date of last seizure.

Definitions:

Grades of Recommendations

A: At least one meta-analysis, systematic review of randomised controlled trials (RCTs), or randomised controlled trial rated as 1++ and directly applicable to the target population; or

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rate as 2++

D: Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Good Practice Points: Recommended best practice based on the clinical experience of the guideline development group.

Levels of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies, e.g. case reports, case series

4: Expert opinion

CLINICAL ALGORITHM(S)

An algorithm for treatment after first tonic-clonic seizure is provided in the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Diagnosis

- Electroencephalography (EEG) is often helpful in the diagnosis and classification of epilepsy. A normal EEG does not exclude a diagnosis of epilepsy. A single routine EEG recording will show definite epileptiform abnormalities in 29-38% of adults who have epilepsy. With repeat recordings this rises to 69-77%. The sensitivity is improved by performing an EEG soon after a seizure, and by recordings with sleep or following sleep deprivation.

  In a patient in whom the clinical history suggests an epileptic seizure but is not conclusive, the prevalence of epilepsy will be high. The finding of epileptiform abnormalities is specific, and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, such as syncope, the prevalence of epilepsy will be low, and any epileptiform abnormalities are more likely to be incidental. The test should not be performed in this circumstance.

  EEG can aid classification of epileptic seizures and epilepsy syndromes. The finding or not of a photoparoxysmal response can allow appropriate advice to be given. If performed within the first few weeks after a first seizure, EEG has prognostic value; patients with epileptiform abnormalities are more likely to have a second attack.

- Brain imaging detects lesions in 21-37% of patients presenting with epilepsy. Such lesions require treatment in only a small minority, but their detection may have implications for future management should the epilepsy become intractable. Idiopathic generalised epilepsies are not associated with an increased prevalence of brain lesions.
- Magnetic resonance imaging (MRI) scanning is the current standard of reference in the investigation of patients with epilepsy. Routine MRI brain scanning using simple standard sequences will detect lesions (e.g., small tumours, vascular malformations and cortical dysplasia) that are not detected by computed tomography (CT) scanning. MRI carried out for the assessment of drug-resistant epilepsy requires specialised protocols and expertise (e.g., to detect hippocampal sclerosis).

Management

- Blood level monitoring should be undertaken to answer a specific clinical question; does imperfect adherence to the treatment schedule explain the poor seizure control? Specialist knowledge is required to interpret assay results as the pharmacokinetics of some AEDs are non-linear and because of the pharmacokinetic interactions that may take place. This is particularly important given the lack of a useful "target range" for the majority of AEDs.
- People with learning disability and epilepsy should have access to the same range of investigations and treatment as the rest of the population. The high prevalence of epilepsy associated with learning disability is at its greatest (about 50%) in people with severe disability and cerebral palsy. Quality of life may be affected because of injuries sustained during seizures and because of the side effects of medication. An excess mortality has also been reported. In some adults who have learning disability it may be difficult to distinguish epilepsy from psychiatric illness, emotional and behavioural outbursts. Where doubts exist, video recording of the episode may help to secure diagnosis, with appropriate consent. Clinical guidelines exist for the management of epilepsy in adults with an intellectual disability. Treatment may need to be given under the provisions of the Adults with Incapacity (Scotland) Act 2000 if the person cannot give informed consent. Seizure freedom is an appropriate endpoint for many patients with learning disability and epilepsy.
- Information about the effects of the menopause on epilepsy is limited but there is evidence to suggest that some women experience an increase in seizure frequency at this time. Hormone replacement therapy (HRT) may improve seizure control in those who previously experienced catamenial epilepsy (seizures with menstruation) but others may experience an increase in their seizure frequency on hormone replacement therapy. The benefit of hormone replacement therapy (oestrogen with or without progesterone) in reducing the risk of osteoporosis and hip fracture is well recognised. Women who have taken AEDs are known to be at increased risk of hip fractures.

Treatment

- Whether to treat a single seizure or not is largely decided by the risk of further seizures (refer to Annex 2 of the original guideline document). Estimates of recurrence risk vary. Highest recurrence rates (up to 90%) are seen in patients with epileptic discharges on EEG or congenital neurological deficits. Lowest rates (13-40%) are associated with acute symptomatic seizures (provoked) or patients with a normal EEG and no identifiable cause for seizures. Overall the risk is 30-40%; this is greatest in the first twelve months and falls to <10% after two years.

  Treatment with antiepileptic drugs (AEDs) reduces the risk of recurrence by half. Early treatment with AEDs does not appear to alter the prognosis of epilepsy, which is best predicted by the number of seizures in the first six months after diagnosis and response to first AED.

- Comparative, randomised, double-blind trials in patients with newly-diagnosed partial and generalised tonic-clonic seizures suggest similar efficacy for phenytoin, carbamazepine, sodium valproate, lamotrigine and oxcarbazepine. The newer AEDs, lamotrigine and oxcarbazepine seem to be

better tolerated and may produce fewer long term side effects and adverse interactions. Sodium valproate and lamotrigine also have efficacy for absence and myoclonic seizures but lamotrigine can worsen myoclonus in some cases. Ethosuximide has been used for absence seizures in children for many decades. Lamotrigine may have advantages for adolescents, young women and the elderly because it is well tolerated, has a favourable cognitive and behavioural profile, does not induce the metabolism of lipid-soluble drugs (such as the hormonal components of the oral contraceptive agent) and does not lead to weight gain.

- Improvement in seizure control may be obtained by combining AEDs. Choice of AED combinations should be guided by side effect profile and drug interactions. There is some evidence that combining AEDs which have different mechanisms of action may enhance effectiveness e.g., lamotrigine with sodium valproate but not with carbamazepine or phenytoin.
- Emergency treatment should be sought or given by carers of people with epilepsy once a seizure has persisted, or there are serial seizures, for more than five minutes. Generalised tonic-clonic status epilepticus is a medical emergency with significant morbidity and mortality, which can often be attributed to inadequate or delayed treatment. Other types of status epilepticus (including simple partial, complex partial and absence status epilepticus) are often associated with delayed diagnosis and treatment, but have a much lower risk of morbidity. Prompt and accurate differentiation of status epilepticus from pseudo-status epilepticus and other non-epileptic disorders is crucial if inappropriate treatment and iatrogenic morbidity are to be avoided. EEG recording may be necessary to confirm the diagnosis and to assess control, when seizures are clinically subtle (e.g., in partial status, or following treatment of tonic-clonic status epilepticus).
- Intravenous lorazepam and diazepam are both effective and safe in controlling tonic-clonic status epilepticus, when administered by paramedics, prior to transport to hospital, with a trend in favour of lorazepam. Intravenous lorazepam, phenobarbital and diazepam plus phenytoin are all effective initial treatments on hospital admission, with a trend again in favour of lorazepam, which is significantly more effective than phenytoin alone. Lorazepam has the advantage over diazepam of a much shorter duration of action, but its use in the community is limited by the need for refrigerated storage. There should be a high level of awareness of the risk of respiratory depression. Additional maintenance treatment is required following initial use of either benzodiazepine. Fosphenytoin is less irritant to veins than phenytoin and can be administered more rapidly (but still needs to be given slowly).

POTENTIAL HARMS

Antiepileptic Drug Side Effects

- Antiepileptic drug (AED) side effects are common and a major cause of drug withdrawal. Most are mild but a minority can be life threatening. Accurate data on the prevalence of adverse drug reactions (ADRs) with long term AED treatment is scarce; almost all reports refer to short term clinical trials and, as experience with vigabatrin and visual field defects has shown, long term surveillance is needed to identify all ADRs. The elderly are more sensitive to AED side effects due to altered pharmacokinetics.

- Many AED side effects are dose-related and predictable. These can be minimised by gradual escalation of dose, with dose reduction if symptoms persist. Use of slow release carbamazepine can reduce peak dose-related side effects of dizziness and blurred vision.
- Idiosyncratic drug reactions usually occur in the first weeks of treatment and are potentially serious. Rash is the most common, occurring in up to 10% of patients on carbamazepine, phenytoin or lamotrigine. Most rashes are mild and resolve promptly on discontinuation of the AED, but severe cutaneous reactions are seen in up to 1:1,000 patients. This incidence is increased if the initial dose is increased rapidly.
- The life-threatening AED hypersensitivity syndrome of fever, rash, lymphadenopathy and multiorgan failure occurs in up to 4.5:10,000 patients, mostly with carbamazepine, lamotrigine or phenytoin. It is important to note that cross sensitivity occurs between these AEDs in up to 70% of patients.
- Minor blood dyscrasias are associated with many AEDs; the majority (mild leucopaenia with carbamazepine, thrombocytopaenia with valproate) require no action. Severe blood dyscrasia occurs in 6:10,000 patients but there is no evidence to suggest that routine monitoring can reduce this risk.
- Hyponatraemia (sodium <135 but usually >125 mmol/L) is seen in about 20% of patients taking carbamazepine or oxcarbazepine; it is usually well tolerated and of no significance. Elevation of liver enzymes (delta-glutamyl transferase 90%, alkaline phosphatase 30%) is seen in people taking enzyme-inducing AEDs and is usually of no clinical significance. Clinical symptoms have been shown to be more useful than routine monitoring of liver function in identifying the onset of serious ADRs.
- Acute psychotic reactions are seen occasionally with newer AEDs, particularly in those patients with a previous history of psychiatric disease; withdrawal from the drug usually results in recovery.
- Weight gain is seen with many AEDs but significant (>10% body weight) weight gain is associated particularly with valproate. Topiramate can cause weight loss.
- Sedation and dizziness are common complaints of patients starting AED therapy but usually resolve with time. Sedation may be less with the newer AEDs. Many patients on long term AED therapy report cognitive side effects but studies to confirm this have been contradictory and confounded by the effects of chronic epilepsy. Polytherapy is probably associated with more cognitive side effects than monotherapy.
- Osteopenia, osteomalacia and increased risk of hip fracture have been associated with AED use but their aetiology is likely to be multifactorial.
- AED withdrawal was associated with an increased risk of seizure recurrence, which was influenced by the duration of seizure freedom, the history of seizure types, the occurrence of one or more seizures after the start of treatment and whether one, or more than one, AED was being taken. The data from the study were used to develop a prognostic index for seizure recurrence. This has been used to calculate the risks of seizure recurrence with continued treatment or with slow AED withdrawal (Refer to tables 2 and 3 in the original guideline document). An abnormal EEG at the time of entry into the study was associated with only a small increased risk of seizure recurrence. Since this is unlikely to influence a decision about whether to withdraw AED treatment or not in adults, EEG recording is not necessary for an informed decision to be made. The higher risks of seizure recurrence with a history of myoclonus reflect the high risk of seizure recurrence following

AED withdrawal in juvenile myoclonic epilepsy. The prognostic index has not been validated on an external population, and should be used with caution.

- Important factors influencing a decision about AED withdrawal in adults include driving, employment, fear of further seizures, risks of injury or death with further seizures and concerns about prolonged AED treatment. The Driver and Vehicle Licensing Agency recommends that driving should cease during the period of AED withdrawal and for six months afterwards, and for many this factor alone may lead to a decision to continue treatment.

Risks to the Fetus from Maternal Epilepsy and Antiepileptic Drugs

- Seizure frequency increases during pregnancy in between a quarter and a third of women due to a number of factors including changes in pharmacokinetics of AEDs and poor adherence to treatment because of concerns about adverse effects on the fetus.
- The long term effect of tonic-clonic seizures on the fetus is not well established although the associated hypoxia and acidosis may adversely affect the obstetric outcome, particularly if the seizures are prolonged. Risks to the woman of injury and, rarely, death in a seizure remain in pregnancy.
- Major and minor fetal malformations occur more commonly in infants exposed to AEDs during pregnancy. The overall risk of major fetal malformation in any pregnancy is approximately 2%. This increases two to three fold in women taking a single AED. Current data suggest that the risk with valproate may be higher than with carbamazepine or lamotrigine. Polytherapy, particularly with certain combinations of drugs, carries a much higher risk (up to 24% in women taking four AEDs).
- The most common major malformations associated with established AEDs are: neural tube defects (valproate 3%, carbamazepine 1%), orofacial defects, congenital heart abnormalities and hypospadias. The risk of minor malformations including hypertelorism, epicanthic folds and digital hypoplasia is increased with AED therapy in pregnancy.
- "Fetal anticonvulsant syndromes" comprising typical dysmorphic craniofacial appearances and a variety of musculoskeletal abnormalities have been described in association with AED treatment in pregnancy. Although individual drugs have been associated with specific patterns, there is overlap between them and genetic factors may influence susceptibility.
- Whether AEDs taken during pregnancy can affect the child's intellectual development is uncertain but concern about the effects of valproate on infant development has recently been raised.
- At present there is insufficient evidence on which to base advice about the risks of most of the newer AEDs (gabapentin, levetiracetam, tiagabine, topiramate, vigabatrin) in pregnancy. Current data on lamotrigine show a malformation rate of 3% (95% confidence interval 1.5-5.7).
- Many pregnancies in women with epilepsy are unplanned, very few women take folate in the correct dose at the appropriate time and advice given about malformation risk and folate is often forgotten. Women taking AEDs, particularly valproate, are at greater risk of having a child with neural tube defects (NTD) and other malformations which may be related to altered folate metabolism. It is recommended that all women should take daily folic acid from preconception and during the first trimester of pregnancy to reduce the incidence of NTD. While there is no evidence to show that folate can reduce the incidence of AED-associated malformations, current guidelines

recommend that a high dose of folate, 5 mg daily, be given from pre-conception to the end of the first trimester.
- Current guidelines recommend maternal vitamin K_1 supplementation with phytomenadione 10 mg daily from 36 weeks of pregnancy for all mothers taking enzyme-inducing AEDs (refer to table 6 of the original guideline document). However, the small risk of haemorrhagic disease of the newborn is not increased in infants of mothers taking enzyme-inducing AEDs provided the infant receives 1 mg vitamin K_1 intramuscularly at birth.

CONTRAINDICATIONS

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Complementary Therapy for Epilepsy

Patients should be asked if they are using any complementary medicines and warned about the possibility of adverse effects. Problems may arise with the use of some herbal medicines because of interaction with prescribed medication. The potential reduction of the plasma concentrations of carbamazepine, phenobarbital and phenytoin should be noted if St John's Wort is used concomitantly. The British National Formulary advises against this. Caution is also advised in the use of evening primrose oil but the evidence for this is less robust.

Some aromatherapy preparations (e.g., hyssop, rosemary, sweet fennel, sage and wormwood) may have an alerting effect on the brain and so may exacerbate seizures.

Drugs which Exacerbate Epileptic Seizures

Drugs may occasionally precipitate seizures particularly in patients with epilepsy or other risk factors. Commonly used drugs are listed below (causality is not always certain and may be multifactorial).

Mechanisms for triggering seizures may include:

- Lowering of seizure threshold - this is usually dose/plasma concentration dependent and factors such as renal impairment (e.g., pethidine) or co-administration of interacting drugs (e.g., ciprofloxacin/theophylline) may contribute
- Decrease in antiepileptic drug (AED) levels via pharmacokinetic drug interactions (e.g., hepatic microsomal enzyme induction with rifampicin)
- Effects secondary to other medical causes precipitated by drugs e.g., drug-induced hyponatraemia or serotonin syndrome
- Individual AEDs which themselves may cause worsening of some types of seizures
- Drug withdrawal e.g., from AEDs, alcohol, benzodiazepines, barbiturates and baclofen

Drugs which May Precipitate Epileptic Seizures

Aminophylline/theophylline

Amphetamines

Analgesics e.g., tramadol

Antibiotics e.g., penicillins, cephalosporins, quinolones

Antidepressants

Anticholinergics e.g., benztropine

Anti-emetics e.g., prochlorperazine

Antipsychotics e.g., chlorpromazine

Baclofen

Bupropion [Zyban]

Cholinesterase inhibitors e.g., donepezil

Ciclosporin

Cocaine

Isoniazid

Ketamine

Lidocaine (lignocaine)

Lithium

Mefloquine

Methylene dioxymethamphetamine (ecstasy)

Non-steroidal anti-inflammatory drugs (NSAIDs) (especially in combination with quinolone antibiotics)

Opioids e.g., diamorphine, pethidine

Oral contraceptives

Vincristine

A wide variety of drugs have been reported to precipitate or potentiate seizures in patients with or without a history of epilepsy. This does not preclude their use when indicated in patients with epilepsy and supported by a risk-benefit assessment. Common examples include:

- Antidepressants, when a selective serotonin re-uptake inhibitor (SSRI, e.g. sertraline, citalopram) may be a reasonable choice
- Antipsychotics, when drugs with lower seizure risk such as haloperidol, risperidone, sulpiride should be used in preference to drugs thought to have higher risk such as clozapine and chlorpromazine
- Antimalarials, when chloroquine and mefloquine are unsuitable for malaria prophylaxis. The current guidelines from the Malaria Reference Laboratory (included in the British National Formulary) should be consulted to choose an appropriate alternative.

QUALIFYING STATEMENTS

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- This guideline is not intended to be construed or to serve as a standard of medical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.
- The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor, following discussion of the options with the patient, in light of the diagnostic and treatment choices available. However, it is advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of local National Health Service (NHS) organisations and is an essential part of clinical governance. It is acknowledged that not every guideline can be implemented immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit. Managed clinical Networks for epilepsy are being developed.

Key points for audit are identified in the original guideline document.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70). [295 references]

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. Update to printed guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004 Jun 7. 3 p. [1 reference]

ADAPTATION

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GUIDELINE COMMITTEE

Not stated

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Scottish Intercollegiate Guidelines Network (SIGN) guideline development groups are required to complete a declaration of interests, both personal and non-personal. A personal interest involves payment to the individual concerned, e.g., consultancies or other fee-paid work commissioned by or shareholdings in the pharmaceutical industry; a non-personal interest involves payment which benefits any group, unit or department for which the individual is responsible, e.g., endowed fellowships or other pharmaceutical industry support. SIGN guideline group members should be able to act as independently of external commercial influences as possible, therefore, individuals who declare considerable personal interests may be asked to withdraw from the group. Details of the declarations of interest of any guideline development group member(s) are available from the SIGN executive.

GUIDELINE STATUS

This is the current release of the guideline.

Any amendments to the guideline will be noted on the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

Electronic copies of Addendum: Available from the SIGN Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Quick reference guide: Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 2 p. Available in Portable Document

Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

- SIGN 50: a guideline developers' handbook. Edinburgh (UK): Scottish Intercollegiate Guidelines Network. (SIGN publication; no. 50). Available from the SIGN Web site.
- Appraising the quality of clinical guidelines. The SIGN guide to the AGREE (Appraisal of Guidelines Research and Evaluation) guideline appraisal instrument. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network, 2001. Available from the SIGN Web site.
- A background paper on the legal implications of guidelines. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network.

PATIENT RESOURCES

The following is available:

- Information for discussion with patients and carers. In: Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70).

Electronic copies: Available from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on November 20, 2003. The information was verified by the guideline developer on January 16, 2004. This NGC summary was updated by ECRI on September 28, 2004. The information was verified by the guideline developer on January 26, 2005.

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